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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,547	10/17/2001	Jim Wells	SUNESIS.002DV1	8070

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 12/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Advisory Action	Application No.	Applicant(s)
	09/981,547	WELLS ET AL.
	Examiner	Art Unit
	Jon D Epperson	1639

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *Please see attached sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *58,59,61,65,81-89,93,95 and 96*.

Claim(s) withdrawn from consideration: *62-64,66,90-92 and 94*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

ADVISORY ACTION

Status of the Application

1. The Response filed November 16, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 58, 59, 61-66 and 81-96 were pending. No claims were added, amended or canceled. Therefore, claims 58, 59, 61-66 and 81-96 are still currently pending.

4. Claims 62-64, 66, 90-92 and 94 are drawn to non-elected species and/or inventions and thus these claims are/remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

Maintained Rejections

Claim Rejections - 35 USC § 103

5. Claims 58, 59, 61, 65 and 81-89, 93, 95 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (WO 98/11436) (Date of Patent is **March, 1998**) (see IDS, entry No. 9) and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. **1996**, pages 119-126).

For ***claims 58, 86-87***, Kim et al. (see entire document) disclose a method for identifying a ligand that binds to a target protein with the greatest affinity by employing a combinatorial library of non-oligomeric organic compounds using "tethering" techniques (see Kim et al., page 1, paragraph 1; see also page 2, paragraphs 1-2). For example, Kim et al. disclose **[a]** combining said target protein with a library containing at least two non-oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond under disulfide exchange conditions, in the presence of a reducing agent (e.g., see Kim et al., see also page 11, paragraph 2, "As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used, potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond"; see also page 17, paragraph 1 disclosing the use of reducing agents, "non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione"). Furthermore, Kim et al. disclose the formation of a target protein-ligand conjugates (e.g., see Kim et al., claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also page 28, paragraph 1, "This experiment illustrates under conditions wherein a specific interaction between a target molecule and ligand can take place, preferential formation of

disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed"). Furthermore, Kim et al. disclose that the target-ligand conjugate can be separated from the mixture (e.g., see Kim et al., page 3, lines 24-26, "Optionally, the complex of the ligand specifically bound to the target molecule can be separated or removed from the library or collection").

In addition, Kim et al. disclose **[c-d]** the detection of the "most abundant" target protein-compound conjugates and the identification of the non-oligomeric organic compounds present in said conjugates having the "greatest relative affinity" (e.g., see Kim et al., page 17, lines 16-25, "The direct thermodynamic relationship also provides an alternative strategy for identifying ligands from a combinatorial library; molecules that bind with ***higher affinity*** will necessarily increase the effective concentration of the other members of the binding pair to a greater extent. Thus, in this embodiment, tethered ligands that bind with higher affinity will have disulfide bonds that are ***more resistant to reduction*** by external reducing agents, such as reduced glutathione"; see also Example 1, especially page 26, last paragraph wherein Glutathione is used in different "ratios" to determine the ligand with the highest affinity, "The biotinylated SH3 domain derivatives and the corresponding synthetic linkers (SH3 : linker; 1:10) are incubated with the library of compounds, in Tris buffer (10 mM, pH 7.5), in the presence of a redox system (e.g., reduced glutathione (GSH) and oxidized glutathione (GSSG) ***at various ratios***"). In other words, only the non-oligomeric organic ligands with the "highest affinity" will remain resistant to the highest "ratios" of reduced/oxidized glutathione. Consequently, the method would also identify the most abundant target protein-compound conjugate

because, at least for the highest ratios of reduced/oxidized glutathione, the conjugate formed using the "non-oligomeric organic compound having the greatest relative affinity" would be the only one that exists at the higher rations or reduced/oxidized glutathione. Finally, Kim et al. disclose "determining the identity" of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al., abstract, "Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands"; see also Summary of the Invention; see also page 8, lines 18-20).

For ***claims 59, 61, 88 and 89***, Kim et al. does not explicitly state that the ligands are "less than about 2000 daltons in size" or "less than 1500 daltons " or "less than 750 daltons" (see claims 58, 59 and 61), but Kim et al. does disclose ligands selected from the group consisting of "small organic molecules, pharmaceuticals, toxins" (see Kim et al., page 21, lines 15-20; see also claim 3 further disclosing "steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin"), which would encompass molecules that are less than 750 daltons in size. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 65 and 93***, Kim et al. does not explicitly state that the target protein is a "TNF receptor" (e.g., see claim 65), but Kim et al. does disclose ligands that are "membrane proteins", which would encompass proteins like TNF receptors because TNF receptors are "membrane proteins" (e.g., see claims 12, 43). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray,* 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 81, 82,*** Kim et al. teach obtaining a target protein comprising a –SH group, masked –SH group, or activated –SH group (e.g., see Kim et al., claims 1-2, "target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a <u>free sulfhydryl group</u> [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange"; see also page 3, paragraphs 2-3; see also page 11, line 11 wherein a "cysteine" residue is disclosed).

For ***claims 83-85, 95 and 96***, Kim et al. do not explicitly state that the library must comprise "at least 25 members" or "at least 100 members" (see claims 84-85), but Kim et al. do state that libraries are produced using the split and pool synthesis techniques taught by Lam (e.g., see Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J., "A new type of synthetic peptide library for

identifying ligand-binding activity" Nature **1991**, 354, 6348, 82-4), which teaches the formation of libraries with greater than 100 members. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray,* 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Kim et al. differ from the claimed invention as follows:

For ***claim 58 and 86***, Kim et al. is deficient in that it does not specifically teach the use of mass spectrometry.

However, Siuzdak teaches the following limitations that are deficient in Kim et al.:

For ***claims 58 and 86***, Siuzdak (see entire document) teaches the use of electrospray mass spectrometry to study both "non-covalent" and "covalent" antibody-antigen interactions including fragmentation techniques like MS^2 and MS^3 (see pages 119-126, especially figures 6.3-6.6 and Table 6.1).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" target/ligand interactions using the method steps as taught by Kim et al. in conjunction with the mass spectrometer techniques as taught by Siuzdak because Siuzdak explicitly shows that the technique can be applied to both "covalent" and "non-covalent" including antibody-antigen interactions (see Siuzdak, figures 6.3, 6.5; see

especially paragraph bridging pages 125-126, "Electrospray mass spectrometry has also demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction"), which would encompass the "antibody-antigen" complexes disclosed by Kim et al. (e.g., see Kim et al., page 4, lines 7-8 disclosing antibody-antigen reactions; see also lines 18-19 disclosing both "covalent" and "non-covalent" interactions). Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has "demonstrated its potential" for these systems (see Siuzdak, page 126, paragraph 1).

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak et al. with the "antibody-antigen" complexes as described by Kim et al. because Siuzdak et al. discloses that BOTH "covalent" and "non-covalent" interactions can be measured (and distinguished) using a mass spectrometer (see Siuzdak et al., page 123, paragraph 3, "Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials (<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al. to work the modified antibodies must bind "covalently" to their respective antigens (see Kim et al., figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on the modified antibody).

Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a "known" ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified ligand is truly able to bind to its respective target via a "covalent" bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the "modified" ligands and/or targets as disclosed by Kim et al. with electrospray mass spectroscopy as disclosed by Siuzdak et al. to find modified ligands that can "covalently" bind to the targets as opposed to any unwanted "non-covalent" interactions that might occur.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen (e.g., see figures 6.3 and 6.5).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[1] Applicants argue, "Mass spectrometry would not have been the method of choice for addressing this problem [detecting the most abundant target protein-ligand conjugate from among a potentially large number of conjugates in a library], since one skilled in the art would have anticipated significant difficulties arising from the presence of a plurality of conjugates ...

and from the fact that the molecular weights of the conjugates present in the mixture are likely to be close to each other, and therefore difficult to distinguish" (e.g., see 11/16/04 Response, page 4, last two paragraphs).

[2] Applicants argue, "The skilled artisan would have been more inclined to eliminate all but one conjugate, which can then be detected, for example, by antibody-based detection methods, as Kim et al. appears to suggest" (e.g., see 11/16/04 Response, page 4, last paragraph; see also page 5, paragraph 1; see also pages 6-7, especially page7, paragraph 3, "Combining the teaching of Kim et al. with ... Siuzdak et al., would at best result only in a method in which a single 'target protein-compound conjugate,' which is not present in a mixture, is detected by mass spectrometry").

[3] Applicants argue, "There is no mention of mass spectrometry as a detection method anywhere in Kim et al." (e.g., see 11/16/04 Response, page 4, middle paragraph).

[4] Applicants argue, "There is no disclosure, suggestion or hint in Siuzdak et al. that mass spectrometry could be used to detect and a particular complex between a target protein and an unknown ligand of the protein in a mixture, comprising a plurality of related molecules, and to identify the ligand in the mixture" (e.g., see 11/16/04 Response, paragraph bridgining pages 5-6).

[5] Applicants argue that there is no motivation to combine (e.g., 11/16/04 Response, page 6, section 3).

[6] Applicants argue that there is no "reasonable expectation" of success (e.g., see 11/16/04 Response, page 7, last paragraph).

[7] Applicants argue that it is impermissible to use "hindsight reconstruction" when making a rejection (e.g., see 11/16/04 Response, page 7, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Applicants' arguments are entirely unsubstantiated and contrary to the vast majority of publications known in the prior art (e.g., see ***References Illustrative of the State of Prior Art*** below). Mass spectrometry was "routinely" applied to almost every conceivable area of chemistry including protein-ligand interactions both separately and as mixtures (e.g., see representative examples below; please also note that a simple search for "mass spectrometry" on Google turned over 1.3 million hits and a simple search for patents using mass spectrometry turned up 1,153 hits for 1997 alone; see also reference (1) below wherein mass spectrometry is applied to mixtures and libraries). Thus, a person of skill in the art would have "routinely" turned to this technique (i.e., this would have been the "obvious" choice).

In addition, the Examiner notes that Applicants provide no evidence for their assertion that "significant difficulties arising from the presence of a plurality of conjugates" would have been realized because the conjugates "are likely to be close to each other [in terms of their molecular weights]." However, even if *assuming arguendo* that the molecular weights were close as purported by Applicants, a person of skill in the art would have been even <u>more motivated</u> to use mass spectrometry because this technique was known to have <u>outstanding resolution</u> i.e., no other analytical technique could provide better resolution than mass spectrometry (e.g., see references (2) and (3) below). Thus, Applicants' assertion is simply not justified.

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., analyzing components in the mixture "simultaneously" i.e., in the presence of other conjugates) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, Applicants use of "comprising" terminology does not preclude "analyzing the mixture" by first separating the components and then subsequently feeding said components through a mass spectrometer. Nothing in the claims requires that the components of the mixture be analyzed "simultaneously" (i.e., in the presence of other conjugates) as purported by Applicants.

In addition, the Examiner notes as above that mass spectroscopy was widely used in almost every conceivable area of chemistry and thus Applicants' assertion that a person of skill in the art would shy away from the technique when faced with a "mixture" as opposed to a "single compound" is simply not justified (see section **[1]** above; see also reference (1) below). In fact, the vast majority of samples analyzed by mass spectrometry are "mixtures" of closely related species because column chromatography and other analytical techniques usually cannot separate such closely related species.

[3] In response to applicant's arguments against the Kim et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[4] The Examiner contends that "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

[5] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has "demonstrated its potential" for these systems (see Siuzdak, page 126, paragraph 1).

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak et al. with the "antibody-antigen" complexes as described by Kim et al. because Siuzdak et al. discloses that BOTH "covalent" and "non-covalent" interactions can be measured (<u>and distinguished</u>) using a mass spectrometer (see Siuzdak et al., page 123, paragraph 3, "Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials (<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al. to work the modified antibodies must bind "covalently" to their respective antigens (see Kim et al., figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on

the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a "known" ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified ligand is truly able to bind to its respective target via a "covalent" bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the "modified" ligands and/or targets as disclosed by Kim et al. with electrospray mass spectroscopy as disclosed by Siuzdak et al. to find modified ligands that can "covalently" bind to the targets as opposed to any unwanted "non-covalent" interactions that might occur.

[6] The Examiner respectfully disagrees. As stated in section **[1]** above, mass spectrometry was routinely used to analyze protein-ligand interactions and would have been the "method of choice" for this type of application. In addition, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer, for example, antibody-antigen target-ligand interactions (e.g., see figures 6.3 and 6.5).

[7] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

References Illustrative of the State of Prior Art

(1) Jindal et al. (WO/9701755) (International Publication Date is **16 January 1995**) shows mass spectrometry was commonly employed for high throughput screening techniques including identification of target/ligand conjugate "mixtures" and/or "libraries" (e.g., see Jindal et al., abstract; see also field of invention wherein "libraries" or "mixtures" are disclosed; see also page 7, lines 15-23; see especially lines 24-26; see also figure 1, element 44).

(2) Henry et al. (Henrey, K. D.; Williams, E. R.; Wang, B. H.; McLafferty, F. W.; Shabanowitz, J.; Hunt, D. F. "Fourier-transform mass spectrometry of large molecules by electrospray ionization" *PNAS* **1989**, *86*, 9075-9078) demonstrates that "high resolution" spectra could be obtained for a wide range of molecular weights as early as 1989 (e.g., see abstract).

(3) Marshall et al. (Marshall, A. G.; Senko, M. W.; Li, W.; Li, M.; Dillon, S.; Guan, S.; Logan, T. M. "Protein Molecular Mass to 1Da by 13C, 15N Double-Depletion and FT-ICR Mass Spectrometry" *J. Am. Chem. Soc.* **1997**, *119*, 433-434) demonstrates "1 Da" resolution of FT-ICR and also "1 Da" resolution for electrospray under certain circumstances.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
December 11, 2004

BENNETT CELSA
PRIMARY EXAMINER